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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/375,924	08/17/1999	MICHAEL GALLO	ABGX-2-CIP	5797

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/375,924	Applicant(s) GALLO ET AL.	
	Examiner DiBrino Marianne	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003 and 04 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. This Supplemental Office Action is being issued to correct the citation of a reference at item # 5 below. It is otherwise identical to the previous Office Action mailed 11/18/03.

2. Applicant's amendment filed 4/15/03 and 2/4/03 are acknowledged and have been entered.

Claims 52-61 are pending and are being examined.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 52-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/18412 (IDS reference) in view of Kim et al (Scand. J. Immunol. 40, 457-465, 1994, IDS reference), Kim (Eur. J. Immunology 1994, 24: 2429-2434, IDS reference) and known facts disclosed in the instant specification on page 41 at lines 24-30.

WO 96/18412 teaches chimeric proteins comprising IgG hinge region and a half-life increasing polypeptide such as the Fc region of an IgG molecule, the Fc region meaning that IgG terminal domain that is produced upon papain digestion of IgG, i.e., comprises a CH2 and CH3 region (especially abstract, page 9 at lines 4-14, page 10 at lines 18-23). WO 96/18412 also teaches that the entire Fc region can be used, or only a half-life enhancing portion.

WO 96/18412 does not teach wherein the said protein is an antibody with an extended serum half-life comprising a first IgG region capable of binding FcRb and at least a second IgG region capable of binding FcRb, wherein at least second IgG regions confers upon said antibody avidity of binding to FcRb receptor at pH 6.0 greater than that of said antibody lacking said at least second IgG region, said second region capable of binding in a pH dependent manner, and the other limitations recited in the instant claims, nor a method for

extending the serum half-life of an antibody by linking the first and at least second IgG regions to create the antibody of the instant product claims.

Kim et al (SJI) teach the necessity for two functional catabolic sites per Fc for serum persistence, and that the increase in avidity of Fc fragments brought about by the presence of two sites per molecule results in improved binding to protective receptor (i.e., FcRb). Kim et al further teach that tagging of a protein with an Fc-derived fragment containing only one functional catabolic site would be predicted to be ineffective in significantly extending the half-life (especially discussion section). Kim et al teach that regions within both the CH2 and the CH3 domains are involved in catabolic control.

Kim et al (EJI) teach pH dependence, i.e., binding at pH of 6-6.5 and release at pH 7.4, of IgG1 or Fc fragment binding to FcRn (i.e, FcRb) and that the presence of two FcRn binding sites per Fc hinge fragment enhance binding to FcRn. Kim et al teach FcRn site is localized to residues at the CH2-CH3 interface.

The known facts disclosed in the instant specification on page 41 at lines 24-30 are that IgG1 has an additional, i.e., unpaired, cysteine capable of disulfide bond formation.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the serum half life of an antibody by making an antibody comprising the protein taught by WO 96/18412 and further comprising an Fc IgG region capable of binding FcRb in a pH dependent manner as taught by Kim et al (SJI) and Kim et al (EJI). In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a mutated hinge region without the unpaired cysteine disclosed as a known fact in the instant specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a protein with increased serum persistence and avidity of binding to FcRb as taught by WO 96/18412, Kim et al (SJI) and Kim et al (EJI), and because Kim et al (SJI) and Kim et al (EJI) teach the need for two FcRn binding sites to significantly increase half life. One of ordinary skill in the art at the time the invention was made would have been motivated to mutate the hinge region to remove or change the unpaired cysteine in order to insure that no additional reactivity would interfere with increased serum half life or function of the antibody due to disulfide bond formation through the unpaired cysteine.

It is of record in the Office Action mailed 2/16/00 at item #10 that FcRp and FcRn are the same receptor.

5. Claims 52-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/18412 (IDS reference) in view of Kim et al (Scand. J. Immunol. 40, 457-465, 1994, IDS reference), Kim (Eur. J. Immunology 1994, 24: 2429-2434, IDS reference) and WO 97/34631 (IDS reference) and known facts disclosed in the instant specification on page 41 at lines 24-30.

WO 96/18412 teaches chimeric proteins comprising IgG hinge region and a half-life increasing polypeptide such as the Fc region of an IgG molecule, the Fc region meaning that IgG terminal domain that is produced upon papain digestion of IgG, i.e., comprises a CH2 and CH3 region (especially abstract, page 9 at lines 4-14, page 10 at lines 18-23). WO 96/18412 also teaches that the entire Fc region can be used, or only a half-life enhancing portion.

WO 96/18412 does not teach wherein the said protein is an antibody with an extended serum half-life comprising a first IgG region capable of binding FcRb and at least a second IgG region capable of binding FcRb, wherein at least second IgG regions confers upon said antibody avidity of binding to FcRb receptor at pH 6.0 greater than that of said antibody lacking said at least second IgG region, said second region capable of binding in a pH dependent manner, and the other limitations recited in the instant claims, nor a method for extending the serum half-life of an antibody by linking the first and at least second IgG regions to create the antibody of the instant product claims.

Kim et al (SJI) teach the necessity for two functional catabolic sites per Fc for serum persistence, and that the increase in avidity of Fc fragments brought about by the presence of two sites per molecule results in improved binding to protective receptor (i.e., FcRb). Kim et al further teach that tagging of a protein with an Fc-derived fragment containing only one functional catabolic site would be predicted to be ineffective in significantly extending the half-life (especially discussion section). Kim et al teach that regions within both the CH2 and the CH3 domains are involved in catabolic control.

Kim et al (EJI) teach pH dependence, i.e., binding at pH of 6-6.5 and release at pH 7.4, of IgG1 or Fc fragment binding to FcRn (i.e, FcRb) and that the presence of two FcRn binding sites per Fc hinge fragment enhance binding to FcRn. Kim et al teach FcRn site is localized to residues at the CH2-CH3 interface.

WO 97/34631 teaches antibody constant domains can be combined with another immunoglobulin domain or with any other protein, that the Ig constant domains may be expressed in combination with an Fc domain or an entire Fc-hinge domain to produce a recombinant protein with enhanced biological stability (especially paragraph spanning pages 15 and 16 and claims 4, 8, 12, 13, 14).

The known facts disclosed in the instant specification on page 41 at lines 24-30 are that IgG1 has an additional, i.e., unpaired, cysteine capable of disulfide bond formation.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the serum half life of an antibody as taught by WO 97/34631 by making an antibody comprising the protein taught by WO 96/18412 and further comprising an Fc IgG region capable of binding FcRb in a pH dependent manner as taught by Kim et al (SJI) and Kim et al (EJI). In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a mutated hinge region without the unpaired cysteine disclosed as a known fact in the instant specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a protein with increased serum persistence and avidity of binding to FcRb as taught by WO 96/18412, Kim et al (SJI) and Kim et al (EJI), and because Kim et al (SJI) and Kim et al (EJI) teach the need for two FcRn binding sites to significantly increase half life and because WO 97/34631 teaches that Ig constant domains may be expressed with an Fc domain or an entire Fc-hinge domain to produce a recombinant protein with enhanced biological stability. One of ordinary skill in the art at the time the invention was made would have been motivated to mutate the hinge region to remove or change the unpaired cysteine in order to insure that no additional reactivity would interfere with increased serum half life or function of the antibody due to disulfide bond formation through the unpaired cysteine.

It is of record in the Office Action mailed 2/16/00 at item #10 that FcRp and FcRn are the same receptor.

6. No claim is allowed.

7. The reference crossed out in the copy of (mailed with the Office Action of 11/18/03) Form 1449 filed 2/4/03, i.e., Progress in Allergy Vol. 13, S. Karger, NY, 1969, has not been considered because it has not been provide by Applicant. It will be considered in the next Office Action. It would expedite prosecution if Applicant would send in a copy of the reference.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 5, 2004

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